Repeated administration of amphetamine induces a shift of the prefrontal cortex and basolateral amygdala motor function

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Abstract

The role of the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) in the expression of behavioural locomotor sensitization to amphetamine (Amph) has been poorly studied. In the present study, we investigated how lidocaine infused in the mPFC or BLA modulated motor responses to acute and repeated (sensitization) Amph administration. We showed that reversible blockade of mPFC or BLA by lidocaine increased both locomotor and rearing responses to acute Amph, but blocked the expression of behavioural sensitization to Amph. These findings indicate that under free-lidocaine conditions repeated administration of Amph would produce a shift of mPFC and BLA motor function from an inhibitory to a facilitatory role in response to Amph. We propose that this phenomenon may be of major critical importance in the development of drug dependence.

Introduction

Behavioural sensitization in rodents refers to a progressive and persistent enhancement of the locomotor activating and rewarding properties induced by repeated and intermittent administration of psycho-stimulant drugs (Kalivas & Stewart, 1991; Robinson & Berridge, 2003). This well-characterized phenomenon has received considerable attention because of its proposed relevance to psychosis and drug addiction (Featherstone et al., 2007; Kalivas et al., 1998; Robinson & Berridge, 2003). In particular, behavioural sensitization involves alterations in neurotransmission within the dopaminergic mesoaccumbens pathway, which originates in the ventral tegmental area and projects to the nucleus accumbens (NAc). While alterations within the ventral tegmental area initiate behavioural sensitization, i.e. its development, alterations within the NAc mediate its expression (Cador et al., 1995; Kalivas & Weber, 1988; Paulson & Robinson, 1991). Nevertheless, beyond the intrinsic role of the NAc, there is now a growing body of evidence that the excitatory amino-acid neurotransmissions that project to the NAc may also play a critical role in the acute and sensitized responses to amphetamine (Amph) (Chi et al., 2006; David & Abraini, 2003; David et al., 2001, 2004; Karler et al., 1989, 1991; Wolf et al., 1995). In that way, the contribution of the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA), which project to the mesoaccumbens pathway through glutamatergic neurons (Berendse et al., 1992; McDonald, 1996; Sesack & Pickel, 1992; Wallace et al., 1992), has been studied extensively, but no general consensus has yet been established. However, surprisingly from a clinical perspective, and in contrast with the large number of studies that have investigated the role of mPFC and BLA in acute locomotor response and the development of behavioural sensitization to Amph and its derivatives, the contribution of these brain structures in the expression of behavioural sensitization to these drugs of abuse has been poorly studied, using irreversible cytotoxic lesion techniques, which has yielded to inconsistent results (Li & Wolf, 1997; Ramos et al., 2005).
In the present study, we studied the specific role of BLA and the prelimbic part of mPFC in the expression of behavioural sensitization to Amph, by investigating how reversible blockade by lidocaine of the mPFC or BLA modulated the locomotor responses to acute and repeated administration of Amph. Here, we show for the first time, to the best of our knowledge, that repeated administration of Amph results in a shift of mPFC and BLA motor function from an inhibitory to a facilitatory (or at least permissive) role.

Methods
Subjects
All animal-use procedures were in accordance with The Declaration of Helsinki and the French legislation for the use of animals in biomedical experimentation. Male Sprague–Dawley rats (Janvier, France) weighing 225–250 g were used (n=64). They were housed socially by groups of four or six for at least 3 d before surgery, or individually after surgery, in Perspex home cages (30×20×20 cm) at 21±0.5 °C with free access to food and water. Light was maintained on a 12-h light/dark cycle (lights on 20:00 hours). All experiments were performed between 10:30 and 15:30 hours.

Surgical procedures and histology
On the day of surgery, rats were anaesthetized by an intraperitoneal (i.p.) injection of 30 mg/kg pentobarbital. They were then implanted with chronic bilateral stainless-steel guide cannulas (21-gauge), 1 mm above the drug-targeted injection site in the prelimbic mPFC (A+3.7, L 0.8, V–3.8 from bregma) or BLA (A–2.8, L 5, V–8.4 from bregma; Paxinos & Watson, 1998) (see Fig. 1). The guide cannulas of 10-mm (mPFC) or 12-mm (BLA) length were anchored to the skull using stainless-steel screws and dental cement. Stainless-steel wire stylets were inserted into the guide cannulas to prevent occlusion. After surgery, the rats were allowed to recover in the animal facility room for at least 5 d before being used experimentally.

At the end of the experiments, rats were killed by intracardiac infusion of sodium pentobarbital under halothane anaesthesia. The skull, including the brain cannula, was quickly removed and post-fixed in a formalin solution for at least 1 wk. Brain coronal sections (120 mm) were cut and mounted on gelatinized slides, stained with Cresyl Violet (1%), dehydrated with serial alcohol and cleared with xylene, and coverslipped with DPX (Fluka, France). The placements of the cannula tips were checked using a bench microscope.

Drug treatment and injection procedure
Drugs were purchased from Sigma-Aldrich (France) and dissolved in saline solution. d-Amph sulfate (1 mg/kg) was administered intraperitoneally (i.p.) in...
Amphetamine-induced mPFC/BLA motor function shift

Fig. 2. Effect of lidocaine infusion into the medial prefrontal cortex (mPFC) or the basolateral amygdala (BLA) on basal and acute amphetamine (Amph)-induced locomotor and rearing activities. (a) Experimental protocol used: A, Amph; S, saline; L, lidocaine. (b, c) Left: bilateral infusion of lidocaine (100 μg/1 ml per side) on day 22 (D22) into mPFC potentiates 1 mg/kg.ml Amph-induced increased locomotor and rearing activities compared to day 15 (D15). Right: contrasting with this finding, bilateral infusion of saline on day 22 into mPFC did not alter Amph-induced increased locomotor and rearing activities. (d, e) Left: bilateral infusion of lidocaine (100 μg/1 ml per side) on day 22 into BLA potentiates 1 mg/kg.ml Amph-induced increased locomotor and rearing activities compared to day 15. Right: contrasting with this finding, bilateral infusion of saline on day 22 into BLA did not alter Amph-induced increased locomotor and rearing activities. Locomotor and rearing activities are expressed as mean ± S.E.M. of total photocell counts recorded during the 90-min period of testing following saline or Amph administration. Within-group comparisons: * p < 0.05 vs. day 1; # p < 0.05 vs. day 15.

Experimental protocol

Habituation and sham injections

In order to avoid environmental novelty, which is known to enhance the behavioural-activating effects of Amph, the rats were very well habituated to their environmental conditions and experimental protocol. On days -4 and -2 preceding the beginning of the experiments on day 1, the rats were handled for sham i.p. injection and infusion in the mPFC or BLA, which consisted of introducing 6-mm-long cannulas connected to microtubing in the guide cannulas for a 5-min period and then placing the animals in the activity cages.

Effect of lidocaine on acute Amph

The protocol used is shown in Fig. 2a. Both groups, designated lidocaine mPFC acute Amph group and lidocaine BLA acute Amph group, were administered one systemic saline injection and saline infusion into the mPFC or BLA on day 1, one systemic saline injection and lidocaine infusion into the mPFC or BLA on day 8, one systemic Amph and saline infusion into the mPFC or BLA on day 15, and one systemic Amph and saline injection into the mPFC or BLA on day 15, and one systemic Amph and saline injection into the mPFC or BLA on day 15, and one systemic Amph and saline injection into the mPFC or BLA on day 15, and one systemic Amph and saline injection into the mPFC or BLA on day 15.
bilateral infusion of lidocaine into the mPFC or BLA on day 22. Following injections on days 1, 8, 15, and 22, rats were recorded for locomotor and rearing activities.

In order to check whether these findings may result from the so-called ‘one-shot behavioural sensitization’ (Robinson et al. 1982; Vanderschuren et al. 1999) rather than from an effect of lidocaine by itself, we performed similar additional experiments in the absence of lidocaine. Both groups, designated saline mPFC acute Amph group and saline BLA acute Amph group, received one systemic saline injection and saline infusion into the mPFC or BLA on day 1, one systemic saline injection and lidocaine infusion into the mPFC or BLA on day 8, one systemic Amph and saline infusion into the mPFC or BLA on day 15, and one systemic Amph and bilateral saline infusion into the mPFC or BLA. Following injections on days 1, 8, 15, and 22, rats were recorded for locomotor and rearing activities (See Fig. 2a).

**Effect of lidocaine on behavioural sensitization to Amph**

The protocol used is shown in Fig. 3a. On day 1, all groups of animals, designated saline mPFC Amph-sensitized group, lidocaine mPFC Amph-sensitized group, saline BLA Amph-sensitized group, and lidocaine BLA Amph-sensitized group, received one systemic injection of saline solution and bilateral infusion of saline solution into the mPFC or BLA; the rats were then immediately recorded for locomotor and rearing activities. On day 5, all rats received one systemic injection of Amph and bilateral infusion of saline solution into the mPFC or BLA; the rats were then immediately recorded for locomotor and rearing activities. On days 6 and 7, rats received one daily systemic injection of Amph, and were immediately returned to the animal facility; during days 6 and 7, rats were not introduced into the locomotor-activity testing room in order to avoid possible associative learning between Amph and the locomotor-activity testing room, a phenomenon known to play a key role in behavioural sensitization (Anagnostaras et al. 2002). On day 11, all groups received one systemic challenge injection of Amph and bilateral infusion of saline solution (saline mPFC and BLA Amph-sensitized groups) or lidocaine (lidocaine mPFC and BLA Amph-sensitized groups) into the mPFC or BLA; the rats were then recorded for locomotor and rearing activities.

**Measurement of locomotor and rearing activities**

On the days of testing (days 1, 8, 15, 22 for the acute protocol; days 1, 5, 11 for the sensitization protocol), the animals were brought to the motor-activity testing room in their home cages and placed in the activity cages for 60 min. The animals were then returned to their home cages, brought to the injection room, and injected with saline, lidocaine or Amph. Following injections, the animals were returned to the motor-activity testing room, placed in the activity cages and recorded for 90 min. Locomotor and rearing activities were quantified using a bank of eight individual activity cages measuring $30 \times 20 \times 20$ cm, equipped with two horizontal infrared beams located $3$ cm and $13$ cm above the floor across the long axis of the cage (Imetronic, France). Beam interruptions were detected, and recorded over 10-min intervals on a PC.

**Data presentation and statistical analysis**

Scores of locomotor and rearing activities are expressed as the mean ± S.E.M. They were analysed using non-parametric statistics, since, as stated by Siegel & Castellan (1988), there is no alternative for a small sample size other than using a non-parametric statistical test unless the nature of the population distribution is known exactly. Accordingly, within-group comparisons were analysed using Friedman’s non-parametric ANOVA test for more than two groups for paired series. Following a significant $F$ value, post-hoc comparisons were further performed using Wilcoxon’s signed-ranks paired $t$ test, which is the non-parametric version of the $t$ test to be used in the case of two related (paired) samples or repeated measurements on a single and small sample.

**Results**

**Histology**

Figure 1 illustrates the location sites of the cannula tips placed in the mPFC and BLA. No evidence for neurotoxicity and/or morphological changes was seen in the tissue surrounding the cannula tracks. Data from rats with one or two injection sites outside the mPFC or the BLA ($n=18$) were excluded from the data collection and subsequent statistical analysis. The final analysis included 46 animals, with the following number of animals per group: saline mPFC acute Amph group ($n=5$), saline BLA acute Amph group ($n=5$), lidocaine mPFC acute Amph group ($n=6$), lidocaine BLA acute Amph group ($n=6$), saline mPFC Amph-sensitized group ($n=5$), lidocaine mPFC Amph-sensitized group ($n=6$), saline BLA Amph-sensitized group ($n=7$), lidocaine BLA Amph-sensitized group ($n=6$).
activity is expressed as mean ± S.E.M. of total photocell counts recorded during the 90-min period of testing following saline or Amph administration. Within-group comparisons: * p < 0.05 vs. day 1; # p < 0.05 vs. day 5.

Compared to the behavioural responses shown by the animals whose brain cannulas were correctly implanted bilaterally in the mPFC or BLA, those which had inappropriate injection sites exhibited inappropriate locomotor responses, thereby providing ‘negative control groups’ (although no statistical analysis was possible because of the small number of animals excluded per group). The motor responses of these animals were as follows: incorrectly bilaterally implanted saline mPFC (n = 3) and BLA (n = 3) acute rats exhibited very low scores of locomotor and rearing activities, suggesting that non-symmetrical mechanical lesions may have impaired the neural circuits responsible for the motor effects of systemic Amph; incorrectly bilaterally implanted lidocaine mPFC (n = 2) and BLA (n = 2) acute animals showed no increase of the motor effects induced by acute Amph; incorrectly bilaterally implanted saline mPFC (n = 3) sensitized animals exhibited no behavioural sensitization to Amph, confirming that non-symmetrical mechanical lesions may have impaired the neural circuits responsible for the motor effects of systemic Amph; finally, incorrectly bilaterally implanted lidocaine mPFC (n = 2) and BLA (n = 2) sensitized animals showed no blockade by lidocaine of behavioural sensitization to Amph (data not illustrated).

Effect of lidocaine into the mPFC or BLA on acute Amph-induced increased locomotor and rearing activities

Infusion of lidocaine into the mPFC or BLA had no effect on basal locomotion and rearing activity (n = 11, mPFC, locomotor activity: F₈,₆₀ = 2.273, n.s.; Fig. 2b; rearing activity: F₈,₆₀ = 0.495, n.s.; Fig. 2c; BLA, locomotor activity: F₈,₆₀ = 6.31, n.s.; Fig. 2d; rearing activity: F₈,₆₀ = 6.31, p < 0.005; Z = -0.663, n.s.; Fig. 2e). In contrast, rats that received systemic administration of Amph and bilateral lidocaine infusion into the mPFC or BLA showed both increased locomotor and rearing activities in response to the second Amph administration on day 22 compared to Amph-induced increased locomotor and rearing activities measured on day 15 (lidocaine mPFC acute Amph group, locomotor activity: F₈,₆₀ = 37.5, p < 0.0001; Z = -1.992, p < 0.05; Fig. 2b; rearing activity: F₈,₆₀ = 11.574, p < 0.001; Z = -2.201, p < 0.05; Fig. 2c; lidocaine BLA acute Amph group, locomotor activity: F₈,₆₀ = 20.167, p < 0.0001; Z = -2.201, p < 0.05; Fig. 2d; rearing activity: F₈,₆₀ = 22.685, p < 0.0001; Z = -2.201, p < 0.05; Fig. 2e), thereby indicating that infusion of lidocaine into the mPFC or the BLA increases the facilitatory motor effects of acute Amph on locomotor activity and rearing activity.

In order to check whether these findings may result from the so-called ‘one-shot behavioural sensitization’ (Robinson et al. 1982; Vanderschuren et al. 1999) rather than from an effect of lidocaine by itself, we performed similar additional experiments in the absence of lidocaine. Contrasting with the results obtained in rats injected with lidocaine into the mPFC or BLA, the rats that received systemic administration of Amph and bilateral saline infusion into the mPFC or BLA exhibited no further increase in locomotor and rearing activities on day 22 compared to day 15 (saline mPFC acute Amph group, locomotor activity: F₈,₆₄ = 5,
Effect of lidocaine into the mPFC or BLA on the expression of behavioural locomotor sensitization to Amph

As expected, rats that received repeated systemic administration of Amph and bilateral saline infusion in the mPFC or BLA showed increased locomotor activity in response to the Amph challenge (saline mPFC Amph-sensitized group: \( F_{8,64} = 41.089, p < 0.0001; Z = -2.023, p < 0.05 \); Fig. 2b; saline BLA acute Amph group, locomotor activity: \( F_{8,64} = 0.2, \) n.s.; Fig. 2d; rearing activity: \( F_{8,64} = 0.089, \) n.s.; Fig. 2c), thereby demonstrating that our protocol did not induce ‘one-shot behavioural sensitization’.

Effect of lidocaine into the mPFC or BLA on the expression of behavioural locomotor sensitization to Amph

Similar results were obtained with rearing activity, indicating that blockade of behavioural locomotor sensitization by bilateral infusion of lidocaine into the mPFC or BLA did not result from an increase in rearing activity as this may occur in rats treated with higher doses of Amph. Indeed, as shown in Fig. 4, while rats treated with repeated Amph administration and bilateral saline infusion into the mPFC or BLA showed increased rearing hyperactivity in response to the Amph challenge (saline mPFC Amph-sensitized group: \( F_{8,68} = 33.8, p < 0.0001; Z = -2.023, p < 0.05 \); Fig. 4a; saline BLA Amph-sensitized group: \( F_{8,68} = 30.73, p < 0.0001; Z = -2.366, p < 0.02 \); Fig. 4b), those treated with repeated administration of Amph and bilateral infusion of lidocaine into the mPFC and BLA did not (lidocaine mPFC Amph-sensitized group: \( F_{8,68} = 4.327, p < 0.05; Z = 0.734, \) n.s.; Fig. 4a; lidocaine BLA Amph-sensitized group: \( F_{8,68} = 1.5, \) n.s.; Fig. 4b).

Discussion

The aim of the present study was to determine the specific role of BLA and the prelimbic part of the mPFC in the expression of behavioural sensitization to Amph. Previous investigations on the role of mPFC and BLA in the production of locomotor and rearing activities in response to acute Amph have yielded to inconsistent results, with either no effect (Burns et al., 1993; Cador et al., 1999; Schaub et al., 1997; Tschantke & Schmidt, 2000; Wolf et al., 1995) or an inhibitory role (Lipska et al., 1998) or a facilitatory role (Gonzalez et al., 2000; Jaskiw et al., 1990; Lacroix et al., 2000; Woods & Ettenberg, 2004) of these brain structures on the locomotor response to acute Amph. Here, we found that reversible blockade by lidocaine of BLA or the prelimbic part of mPFC potentiated the locomotor-activating properties induced by the acute systemic administration of Amph, thereby indicating that under lidocaine-free conditions the mPFC and BLA would exert an inhibitory tonus on the locomotor-activating properties of acute Amph. Contrasting with these findings, we also found that lidocaine infusion in the mPFC or BLA reduced the increase in locomotor...
and rearing activities in response to repeated administration of Amph, i.e. behavioural sensitization to Amph, a result indicating that under lidocaine-free conditions the mPFC and BLA would exert a facilitatory and necessary action on the expression of behavioural sensitization to Amph. While our results oppose those of Li & Wolf (1997), they are in good agreement with other investigations (Pierce et al. 1998; Ramos et al. 2005). Taken together, our data suggest that repeated injection of Amph results in a shift of mPFC and BLA motor function from an inhibitory to a facilitatory role in response to Amph administration.

Both the mPFC and BLA densely innervate the ventral tegmental area–NAc dopaminergic pathway (i.e. mesoaccumbens pathway), which is known to play a key role in mediating the locomotor response to acute and repeated administration of Amph (Cador et al. 1995; Kelley et al. 1986; Kalivas & Weber, 1988; Paulson & Robinson, 1991), and further share reciprocal connections (McDonald, 1996; McDonald et al. 1996; Vertes, 2004). While acutely increased dopamine release in the mPFC reduces mPFC neurons’ firing rate and further suppresses the activity of BLA projection neurons (Lewis & O’Donnell, 2000; Rosenkranz & Grace, 2001), similar experiments in Amph-pretreated rats have shown that dopamine is less efficacious in inhibiting the firing rate of mPFC neurons (Peterson et al. 2000, 2006), thereby indicating, in good agreement with our findings, a shift in the physiological function of mPFC neurons between acute and repeated administration of Amph. Recent findings have also reported similar mechanisms for BLA by demonstrating that dopamine release, as it may occur following Amph administration, shifts the balance of excitatory and inhibitory transmission in the BLA–mPFC pathway and further produces a net increase of the excitatory influence that the BLA exerts over mPFC neurons (Floresco & Tse, 2007). These data taken together with our findings support a previous proposition that in the sensitized state, there would be a loss of inhibitory tone in the mPFC that would be responsible for a reduction of mPFC-induced inhibitory regulation of BLA (Everitt & Wolf, 2002). Therefore, the resulting enhancement of the excitatory BLA drive to the NAc may contribute to many glutamate-dependent mechanisms in drug effects in the NAc (Rosenkranz & Grace, 2001). Within the NAc the expression of behavioural sensitization in response to glutamatergic inputs is mediated through multiple glutamatergic neurons (Berendse et al. 1992; McDonald, 1996; Sesack & Pickel, 1992; Wallace et al. 1992). Among these receptors, the group II metabotropic glutamatergic (mGlu) receptors might play a key role in the shift of mPFC and BLA motor function from an inhibitory to a permissive role found in the present study. Support for this is the fact that blockade of group II mGlu receptors respectively reduces and augments, in a unique manner, the increase in locomotion activity induced by acute or repeated administration of Amph (Chi et al. 2006; David & Abraini, 2003; Kim et al. 2000). Conversely, activation of group II mGlu receptors reduces behavioural locomotor sensitization to repeated administration of Amph (Kim et al. 2005; Kim & Veiana, 2002).

Previous studies by Jentsch & Taylor (1999) and Bechara (2005) have proposed that the first experience of drug abuse – and then after addiction – can be viewed as the product of an imbalance between two separate, but interacting, neural systems that control decision making: a reflective-planning inhibitory prefrontal cortex system for signalling future prospects, and an impulsive-habit-facilitatory amygdala system for signalling immediate prospects. With this perspective, after a first experience of drug abuse, the decision to re-use or not to re-use drugs would depend on the balance between the reflective inhibitory system and the impulsive facilitatory system, so that in individuals vulnerable to addiction (or forced into becoming addicts) the processes driven by the prefrontal cortex-reflective system that enables one to inhibit action would be dysfunctional because of genetic and/or environmentally induced reasons. In contrast with these models, our findings that inhibition of the mPFC or BLA enhances acute locomotor response to acute Amph and further prevents the expression of behavioural sensitization suggest that both brain regions may play parallel roles in both naive and sensitized rats. To explain this discrepancy, we propose on the basis of the findings reported above (Everitt & Wolf, 2002; Lewis & O’Donnell, 2000; Peterson et al. 2000, 2006; Rosenkranz & Grace, 2001) that the model of Jentsch & Taylor (1999) and Bechara (2005) could be adapted as follows: at the first time of a drug abuse experience (acute Amph), the inhibitory signals of the reflective mPFC system would overcome those of the impulsive-habit-facilitatory BLA system in order to reduce or to block such an unusual immediate experience. Thereafter, the repeated administration/consumption of drugs of abuse would imbalance the systems in favour of the impulsive-habit BLA system whose facilitatory signals would overcome those of the reflective-inhibitory mPFC system, leading to increased drug effects and addiction.

However, at least two alternative hypotheses must be also considered. First, because the mPFC and BLA are known to be involved in associative learning
(Cardinal et al. 2002; Everitt et al. 1999; Jentsch & Taylor, 1999), a possible alternative hypothesis could be that lidocaine administration might have disrupted contextual conditioning associated with Amph administration. Second, the possibility must be also examined that the effects of lidocaine in the mPFC and BLA may have resulted from an Amph-induced increase in stereotypy, a phenomenon known to interfere with locomotion (Vanderschuren et al. 2002; Wolf et al. 1995). However, this is unlikely to be true since our results have demonstrated similar effects of lidocaine injection in both rearing activity, a behavioural response often considered as a stereotypy, and locomotion. Support for this are recent data that have shown no stereotypy during the expression of behavioural sensitization at a challenge dose of 1 mg/kg in animals pretreated with 2.5 mg/kg Amph for five consecutive days (Nordquist et al. 2008).

In conclusion, our data bring new insight on the role and contribution of mPFC and BLA in locomotor responses to acute and repeated Amph administration. Here, we showed that repeated administration of Amph results in a shift of the BLA and prelimbic mPFC motor function from an inhibitory to a permissive role in response to Amph, a phenomenon that may be of major importance in the development of drug dependence. Because the prelimbic part and the infralimbic part of the mPFC are respectively thought to initiate and to inhibit drug of abuse seeking (Peters et al. 2008; Vidal-Gonzalez et al. 2006), it should be of interest using lidocaine-induced reversible inhibition to investigate the role of the infralimbic part of mPFC in the motor responses to acute and chronic Amph.

Acknowledgements
This work was supported by the University of Caen – Basse Normandie, the CNRS, and NNOXe Pharmaceuticals (Canada).

Statement of Interest
None.

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